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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/088,405
Filing Date: July 24, 2002
Appellant(s): CHANDRASEKAR ET AL.

Glenn E. Karta
Reg. No. 30,649
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed June 5, 2008 appealing from the Office action mailed September 6, 2007.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

No amendment after final has been filed.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

U.S. 5,866,561	Ungs	2-1999
U.S. 4,727,064	Pitha	2-1988
U.S. 5,383,332	Fontana	1-1995

U.S. 6,117,911 Grainger et al. 9-2000

O'Brien et al. "Relation between estrogen replacement therapy and restenosis after percutaneous coronary interventions", J. Am. Coll. Cardiol., vol. 28, no. 5, November 1996, pp.111-118.

Bauters et al. "The biology of restenosis", Prog, Cardiovas. Dis., vol. 40, nol. 2, Sept.-Oct. 1997, pp. 107-116.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 112

Claim 24 recites the limitation "therapeutic moiety", which is dependent on claim 1. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 103

(1) Claims 1, 3-4, 8, 10, 12-14, 16-18, 20 and 22-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ungs in view of O'Brien et al., in further view of Bauters et al.

Ungs teaches a method for inducing angiogenesis in blood vessels proximal to stenosed regions, including application of an estrogen compound to the blood vessel walls at a treatment site proximal to or upstream of the stenosis (see abstract, in particular.) Ungs teaches that restenosis following PTCA is a significant problem, and that administration of estrogen to the stenosed, dilated region after PTCA has been suggested for the purposes of preventing restenosis (see column 1, lines 10-20 and 40-52, in particular), and thus teaches administration to an injured site (i.e. one that has been injured by PTCA). Ungs teaches that it is thus desirable to increase perfusion to heart tissue in place of or in addition to PTCA treatment (see column 1, lines 54-65, in particular.) Ungs teaches that a preferred method of treating stenosis involves application with a double walled drug delivery balloon catheter, as well as by coating a stent with an estrogen compound or by puncturing a vessel wall (see column 2, lines 5-45, in particular.) Ungs teaches that preferred estrogen compounds include 17-Beta estradiol (see column 4, lines 1-12, in particular), as in claims 1 and 14. Accordingly, Ungs teaches administration of 17-Beta estradiol in the lumen of a blood vessel having suffered vascular injury. Ungs furthermore teaches single administration of 17-Beta estradiol, as recited in claims 8 and 18, as Ungs teaches the compound can be administered via a stent or balloon catheter. There is no other therapeutic moiety disclosed that can be administered other than the estrogen compound, preferably 17-β estradiol or estradoil (see column 4, lines 1, 10 and 11; claim 1; addresses claim 24).

Ungs does not specifically teach a method of improving reendothelization and vascular endothelial function. Ungs also does not specifically teach administering 17β-estradiol in the specific dosages in an amount effective to improve reendothelization and vascular endothelial function as recited in claims 1, 3-4 and 16-17.

O'Brien et al. teaches estrogen replacement therapy has been associated with a reduction in cardiovascular events and improvement in endothelial function (see abstract, background, lines 1-3). The results of the study suggest that estrogen replacement therapy reduces restenosis after coronary intervention, particularly in patients receiving directional coronary atherecotomy (see page 1117, column 1, conclusion, lines 1-4). In addition, estrogen may prevent restenosis by altering cellular migration and neointimal proliferation after coronary intervention (see page 1115, column 2, paragraph 3, lines 1-3). In vitro, physiologic levels of estrogen have been shown to inhibit proliferation of vascular smooth muscle from the coronary arteries of female pigs (see page 115, column 2, paragraph 3, lines 5-6 to page 1116, column 1, line 1).

Bauters et al. teaches that previous investigations have underscored the principle of cross-talk between endothelial cells and smooth muscle cells. Neointimal thickness is closely related to the presence of a regenerated endothelium. Indeed, intimal areas that are rapidly covered by continuous endothelium are protected from the

accumulation of intimal SMCs (smooth muscle cells), whereas typical intimal hyperplasia occurs in areas where re-endothelialization is delayed. Endothelium, in addition to its well-known role in regulating vessel tone and platelet aggregation, appears to modulate proliferative activity of the underlying SMCs (see page 108, column 2, growth regulatory properties of endothelial cells, lines 1-13). Dysfunctional regenerating endothelium may contribute to the development of thickened intima because of SMC proliferation. There are documented cases that demonstrate retardation of endothelial cell recoverage over damaged as opposed to normal media (see page 109, column 1, lines 3-11).

Although Ungs does not specifically teach a method of improving reendothelization, Ungs teaches a reduction in restenosis. O'Brien et al. also teaches the effect of estrogen such as estrogen replacement therapy (i.e. such as 17β estradiol and its derivatives) on reducing restenosis after injury. O'Brien et al. also teaches some of the mechanistic properties of estrogen in the reduction of restenosis, by inhibiting proliferation of vascular smooth muscle from the coronary arteries. Bauters et al. teaches the connection between restenosis/smooth muscle proliferation and reendothelization, in that there is a cross-talk between endothelial cells and smooth muscle cells. Particularly, neointimal thickness is closely related to the presence of a regenerated endothelium. Indeed, intimal areas that are rapidly covered by continuous endothelium are protected from the accumulation of intimal SMCs (smooth muscle cells), whereas typical intimal hyperplasia occurs in areas where re-endothelialization is

delayed (see page 108, column 2, growth regulatory properties of endothelial cells, lines 1-13). Dysfunctional regenerating endothelium may contribute to the development of thickened intima because SMC proliferation. There are documented cases that demonstrate retardation of endothelial cell recoverage over damaged as opposed to normal media (see page 109, column 1, lines 3-11). In other words, since restenosis is reduced by the inhibition of proliferation of SMCs as taught by O'Brien et al., and the proliferation of SMC's are related to the dysfunctional regenerating endothelium (i.e. reendothelialization) as taught by Bauters et al., then one of ordinary skill in the art would find it obvious to treat a patient with 17β estradiol or its derivatives to improve reendothelialization since Ungs discloses that 17β estradiol reduces restenosis as well as O'Brien discloses that estrogen reduces restenosis.

In regards to improving vascular endothelial function, the above argument applies. Particularly, O'Brien et al. teaches the relationship between estrogen replacement therapy and its known ability to improve endothelial function (see abstract, background, lines 1-3). Since 17β estradiol and its derivatives are known in the art to be used as estrogen replacement therapy, it is obvious that one skilled in the art would administer 17β estradiol to improve vascular endothelial function.

Furthermore, it is noted that as Ungs teaches administering the same compound via the same method as that instantly claimed, and to reduce the incidence of restenosis following a treatment such as PTCA that induces vascular injury, it is

considered that the method of Ungs would necessarily also improve reendothelization and vascular endothelial function in a patient having suffered vascular injury, as recited in the claim.

In regards to the amounts of 17β–estradiol or its derivatives as disclosed in claims 1, 3-4, and 16-18, it is noted that Ungs teaches that 17β-estradiol is a preferred estrogen compound (see column 4, lines 1-11, in particular), and Ungs also teaches various methods of application of the estrogen via catheters, stents, etc, and refers to prior art catheter, for example, that are used for the local administration of drugs (see column 3, lines 1-15, in particular.) Furthermore, it is considered that one of ordinary skill in the art at the time the invention was made would have found it obvious to vary and/or optimize the amount of 17β-estradiol provided in the method, according to the guidance provided by Ungs, to provide the desired treatment, such as the desired reduction in restenosis. It is noted that "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955.)

Regarding claims 12-13 and 22-23, Ungs teaches that restenosis following PTCA is a significant problem (see column 1, lines 10-20, in particular), and teaches that treatment to increase perfusion to heart tissue, such as with estrogen compounds, are desirably performed in place of, or in addition to, PTCA (see column 1, lines 50-65, in

particular.) Accordingly, one of ordinary skill in the art at the time the invention was made would have found it obvious to provide the 17-beta estradiol following or simultaneously with the PTCA, based on the teachings of Ungs, with the expectation of increasing perfusion to heart tissue and for reducing the likelihood of restenosis.

Regarding claims 10 and 20, Ungs teaches that the estrogen can be administered with an ionic carrier (pharmaceutically acceptable carrier) in an iontophoresis method using delivery balloon catheter (see column 2, lines 32-40, in particular.)

(2) Claims 5-7, 11 and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ungs in view of O'Brien et al., in further view of Bauters et al. as applied to claims 1, 3-4, 8, 10, 12-14, 16-18, 20 and 22-24 above, and further in view of Pitha.

Ungs, O'Brien et al. and Bauters et al. teachings are as applied to claims 1, 3-4, 8, 10, 12-14, 16-18, 20 and 22-24 above.

Ungs in view of O'Brien et al. and in further view of Bauters et al. does not specifically teach administration of hydroxypropyl-beta-cyclodextrin (HPCD) as recited in claims 5-7. Ungs in view of O'Brien et al. and in further view of Bauters et al. also

does not specifically teach providing a pharmaceutically acceptable carrier in administering the 17-beta estradiol via stent, as recited in claims 11 and 21.

Pitha teaches that pharmaceutical preparations containing cyclodextrin derivatives have enhanced dissolution properties and thus enhanced absorption by the body (see abstract, in particular.) Pitha teaches that cyclodextrin mixtures effectively solubilize liphophilic drugs in aqueous media (pharmaceutically acceptable carrier), and have low toxicity (see column 2, lines 35-60, in particular.) Pitha demonstrates that estradiol is a drug that exhibits improved solubility in combination with hydroxypropyl-beta-cyclodextrin (see Table I, in particular.) Accordingly, Pitha teaches the benefits in improved solubility and absorption of providing estradiol in combination with hydroxypropyl-beta-cyclodextrin, and in a pharmaceutically acceptable carrier such as aqueous media, as recited in claims 11 and 21 are known.

Regarding the dosage amount recited in claim 7, Pitha teaches that the cyclodextrin additives may generally be utilized in a weight percent of from about 40-60% of the drug solution (see column 2, lines 62-68, in particular.) Pitha furthermore teaches intraperitoneal injection of hydroxypropyl-beta-cyclodextrin into mice was non-fatal at 3.2g/kg, and teaches a lack of oral toxicity of the hydroxypropyl-beta-cyclodextrin (see column 4, line 64 through column 5, line 5, in particular.) Accordingly, it is considered that one of ordinary skill in the art at the time the invention was made would have found it obvious to optimize the amount of hydroxypropyl-beta-cyclodextrin

provided in the medication, according to the guidelines provided by Pitha, to provide the desired solubility and absorption characteristics of the estradiol. It is noted that "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955.)

Accordingly, one of ordinary skill in the art at the time the invention was made would have found it obvious to provide the hydroxypropyl-beta-cyclodextrin and pharmaceutically acceptable carrier of Pitha in the 17-beta estradiol delivery method of Ungs, with the expectation of improving the solubility and absorption of the 17-beta estradiol compound in the patient.

(3) Claims 1, 3-4, 8, 10-14, 16-18, 20-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ungs in view of Fontana, in further view of Grainger et al.

Ungs teaches a method for inducing angiogenesis in blood vessels proximal to stenosed regions, including application of an estrogen compound to the blood vessel walls at a treatment site proximal to or upstream of the stenosis (see abstract, in particular.) Ungs teaches that restenosis following PTCA is a signification problem, and that administration of estrogen to the stenosed, dilated region after PTCA has been suggested for the purposes of preventing restenosis (see column 1, lines 10-20 and 40-52, in particular), and thus teaches administration to an injured site, i.e. one that has

been injured by PTCA. Ungs teaches that it is thus desirable to increase perfusion to heart tissue in place of or in addition to PTCA treatment (see column 1, lines 54-65, in particular.) Ungs teaches that a preferred method of treating stenosis involves application with a double walled drug delivery balloon catheter, as well as by coating a stent with an estrogen compound or by puncturing a vessel wall (see column 2, lines 5-45, in particular.) Ungs teaches that preferred estrogen compounds include 17-Beta estradiol (see column 4, lines 1-12, in particular), as in claims 1 and 14. Accordingly, Ungs teaches administration of 17-Beta estradiol in the lumen of a blood vessel having suffered vascular injury. Ungs furthermore teaches single administration of 17-Beta estradiol, as recited in claims 8 and 18, as Ungs teaches the compound can be administered via a stent or balloon catheter. There is no other therapeutic moiety disclosed that can be administered other than the estrogen compound, preferably 17-β estradiol or estradoil (see column 4, lines 1, 10 and 11; claim 1; addresses claim 24).

Ungs does not specifically teach a method of improving reendothelization and vascular endothelial function. Ungs also does not specifically teach administering 17β-estradiol in the specific dosages in an amount effective to improve reendothelization and vascular endothelial function as recited in claims 1, 3-4 and 16-17.

Fontana teaches administering an effective amount of estradiol derivatives used in the method of inhibiting aortal smooth muscle cell proliferation, particularly restenosis, in humans (see abstract). The effective amount means an amount of compound of the

methods of the present invention which is capable of inhibiting the symptoms of the pathological conditions herein described (see column 5, lines 13-16). The compounds are administered after medical procedures such as angioplasty (see column 5, lines 11 and 12). The compound is combined with a pharmaceutically acceptable carrier from 0.1% to 99.9% by weight of the formulation (see column 5, lines 35-39).

Grainger et al. teaches compounds to treat vascular traumas of differing severity, such as to prevent vascular rejection following graft or transplant, while larger doses are sufficient to treat more extensive vascular trama, such as restenosis following angioplasty (see column 34, lines 4-10). A biodegradable stent with the therapeutic agent impregnated therein can further be coated with a biodegradable coating having the therapeutic agent dispersed therein (see column 38, lines 27-30). Intravascular stents also provide a mechanical means of providing an increase in luminal area of a vessel (see column 38, lines 36-38). Furthermore, the placement of intravascular stents comprising a therapeutic agent which is an inhibitor of smooth muscle cell proliferation can provide increased efficacy by reducing or preventing intimal proliferation. This inhibition of intimal smooth muscle cells and stroma produced by the smooth muscle and pericytes can allow more rapid and complete re-endothelization following the intraventional placement of the vascular stent. The increased rate of re-endothelization and stabilization of the vessel wall following stent placement can reduce the loss of luminal area and decreased blood flow which is the primary cause of vascular stent failures (see column 38, liens 39-50).

Although Ungs does not specifically teach a method of improving reendothelization and vascular endothelial function, Ungs teaches 17β-estradiol reduces restenosis. Fontana teaches that estrogen derivatives reduces restenosis and particularly inhibits aortal smooth muscle cell proliferation. Grainger et al. provides the teaching to connect restenosis, smooth muscle cell proliferation and improving reendothelization and vascular endothelial function. Thus, a method of improving reendothelization and vascular endothelial function is rendered obvious by Ungs in view of Fontana and in further view of Grainger et al.

Furthermore, it is noted that as Ungs teaches administering the same compound via the same method as that instantly claimed, and to reduce the incidence of restenosis following a treatment such as PTCA that induces vascular injury, it is considered that the method of Ungs would necessarily also improve reendothelization and vascular endothelial function in a patient having suffered vascular injury, as recited in the claim.

In regards to the amounts of 17β–estradiol or its derivatives as disclosed in claims 1, 3-4, and 16-18, it is noted that Ungs teaches that 17β-estradiol is a preferred estrogen compound (see column 4, liens 1-11, in particular), and Ungs also teaches various methods of application of the estrogen via catheters, stents, etc, and refers to

prior art catheter, for example, that are used for the local administration of drugs (see column 3, lines 1-15, in particular.) Additionally, Fontana teaches that estradiol derivatives are effective to reduce restinosis in an amount from 0.1% to 99.9% by weight of the formulation (see column 5, lines 35-39). Therefore in light of the discussion above, the amounts would be obvious to one skilled in the art. Furthermore, it is considered that one of ordinary skill in the art at the time the invention was made would have found it obvious to vary and/or optimize the amount of 17β-estradiol provided in the method, according to the guidance provided by Ungs, to provide the desired treatment, such as the desired reduction in restenosis. It is noted that "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955.)

Regarding claims 11 and 21, the use of a stent coated with said 17β-estradiol, and a phraceutically acceptable carrier is obvious because Grainger et al. teaches that the placement of intravascular stents comprising a therapeutic agent which is an inhibitor of smooth muscle cell proliferation can provide increased efficacy by reducing or preventing intimal proliferation. This inhibition of intimal smooth muscle cells and stroma produced by the smooth muscle and pericytes can allow more rapid and complete re-endothelization following the intraventional placement of the vascular stent. The increased rate of re-endothelization and stabilization of the vessel wall following stent placement can reduce the loss of luminal area and decreased blood flow which is

the primary cause of vascular stent failures (see column 38, liens 39-50). Thus, the limitation of claim 21 is taught.

Regarding claims 12-13 and 22-23, Ungs teaches that restenosis following PTCA is a significant problem (see column 1, lines 10-20, in particular), and teaches that treatment to increase perfusion to heart tissue, such as with estrogen compounds, are desirably performed in place of, or in addition to, PTCA (see column 1, lines 50-65, in particular.) Accordingly, one of ordinary skill in the art at the time the invention was made would have found it obvious to provide the 17-beta estradiol following or simultaneously with the PTCA, based on the teachings of Ungs, with the expectation of increasing perfusion to heart tissue and for reducing the likelihood of restenosis.

Regarding claims 10 and 20, Ungs teaches that the estrogen can be administered with an ionic carrier (pharmaceutically acceptable carrier) in an iontophoresis method using delivery balloon catheter (see column 2, lines 32-40, in particular.)

(4) Claims 5-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ungs in view of Fontana, in further view of Grainger et al., and further in view of Pitha.

Ungs, Fontana and Grainger et al. teachings are as applied to claims 1, 3-4, 8, 10-14, 16-18, 20-24 above.

Ungs in view of Fontana and in further view of Grainger et al. does not specifically teach administration of hydroxypropyl-beta-cyclodextrin (HPCD) as recited in claims 5-7.

Pitha teaches that pharmaceutical preparations containing cyclodextrin derivatives have enhanced dissolution properties and thus enhanced absorption by the body (see abstract, in particular.) Pitha teaches that cyclodextrin mixtures effectively solubilize liphophilic drugs in aqueous media (pharmaceutically acceptable carrier), and have low toxicity (see column 2, lines 35-60, in particular.) Pitha demonstrates that estradiol is a drug that exhibits improved solubility in combination with hydroxypropyl-beta-cyclodextrin (see Table I, in particular.) Accordingly, Pitha teaches the benefits in improved solubility and absorption of providing estradiol in combination with hydroxypropyl-beta-cyclodextrin, and in a pharmaceutically acceptable carrier such as aqueous media are known.

Regarding the dosage amount recited in claim 7, Pitha teaches that the cyclodextrin additives may generally be utilized in a weight percent of from about 40-60% of the drug solution (see column 2, lines 62-68, in particular.) Pitha furthermore teaches intraperitoneal injection of hydroxypropyl-beta-cyclodextrin into mice was non-

fatal at 3.2g/kg, and teaches a lack of oral toxicity of the hydroxypropyl-beta-cyclodextrin (see column 4, line 64 through column 5, line 5, in particular.) Accordingly, it is considered that one of ordinary skill in the art at the time the invention was made would have found it obvious to optimize the amount of hydroxypropyl-beta-cyclodextrin provided in the medication, according to the guidelines provided by Pitha, to provide the desired solubility and absorption characteristics of the estradiol. It is noted that "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955.)

Accordingly, one of ordinary skill in the art at the time the invention was made would have found it obvious to provide the hydroxypropyl-beta-cyclodextrin and pharmaceutically acceptable carrier of Pitha in the 17-beta estradiol delivery method of Ungs in view of Fontana and in further view of Grainger et al., with the expectation of improving the solubility and absorption of the 17-beta estradiol compound in the patient.

(10) Response to Argument

> The Appellant argues that the “therapeutic moiety” in claim 24 refers to anything other than “17β-estradiol or a derivative thereof” from claim 1. The scope of claim 24 would be readily ascertained by one of ordinary skill in the art, and thus is not indefinite.

The Examiner agrees and therefore withdraws the 35 U.S.C. 112, second paragraph rejection.

> The Appellant argues that Ungs does not teach that administration of estrogen to the stenosed, dilated region after PTCA to prevent restenosis because Ungs is clearly interpreting the work of Hughes et al. and Javitt. Neither Hughes et al. nor Javitt teach administration of estrogen to the stenosed, dilated region (i.e. to an injured site) after PTCA for the purposes of preventing restenosis. Additionally, Ungs teaches away for the present invention by teaching that angiogenesis induction by estrogen could replace PTCA.

The Examiner disagrees because Ungs provides the teaching that it is known in the art that blood vessels are injured and/or that restenosis is common after PTCA, and that treatment and/or prevention is needed. Particularly, Javitt teaches that operative and non-operative procedures injure to a greater or lesser extent the interior wall of the lumen of the blood vessel at the target site, which often leads through a cascade of event to restenosis (see column 1, lines 12-16). Additionally, Ungs teaches that a treatment to increase perfusion to heart tissue in place of, or in addition to PTCA is desirable (see column 1, lines 62-63). Therefore, there is motivation to provide treatment to the injured site of the vessel after PTCA.

Ungs particularly teaches a method for inducing angiogenesis in blood vessels proximal to stenosed regions, including application of an estrogen compound to the blood vessel walls at a treatment site proximal to or upstream of the stenosis (see abstract, in particular.) Ungs teaches that a preferred method of treating stenosis involves application with a double walled drug delivery balloon catheter, as well as by

coating a stent with an estrogen compound such as 17-Beta estradiol (see column 2, lines 5-45, and column 4, lines 1-12.)

Ungs does not specifically teach a method of improving re-endothelization and vascular endothelial function, but the teachings of O'Brien and Bauters et al. are relied upon for the teachings of this limitation.

> The Appellant argues that O'Brien merely suggest several potential mechanisms of action for the ability of estrogens to modulate restonesis in postmenoposal women, and admits that the effect of estrogen on the proliferation of SMCs (smooth muscle cells) have been conflicting. The Declaration by Dr. Stack's establishes that restenosis and reendothelization are two independent events that are affected differently by different compounds, and that it cannot be predicted whether an agent known to prevent or reduce smooth muscle cell (SMC) proliferation and/or to prevent or reduce blood vessel wall thickening will also promote reendothelization. Therefore, there is absolutely no expectation of success that administration of estrogens will have an effect on SMCs proliferation in humans.

The Examiner disagrees because O'Brien et al. clearly teaches that estrogen replacement therapy has been associated with a reduction in cardiovascular events and improvement in endothelial function (see abstract, background, lines 1-3). The results of the study suggest that estrogen replacement therapy reduces restenosis after coronary intervention, particularly in patients receiving directional coronary atherecotomy (see page 1117, column 1, conclusion, lines 1-4). The majority of the studies report that estrogen significantly inhibited neointimal proliferation after arterial balloon injury (see page 1116, lines 1-6). Also, physiologic levels of estrogen have

been shown to inhibit proliferation of vascular smooth muscle from the coronary arteries of female pigs (see page 1115, column 2, paragraph 3, lines 5-6 to page 1116, column 1, line 1). Lastly, O'Brien's study shows that estrogen replacement therapy may reduce restenosis after coronary intervention, and recommends the use of estrogen replacement therapy as a means of preventing restenosis after coronary intervention in future studies (see page 1117, column 1, conclusions). Thus, the O'Brien et al. reference is used to establish that estrogen can reduce restenosis, and improve endothelial function by inhibiting SMCs. Reendothelization is addressed with the teachings of Bauters which is addressed below.

> The Appellant argues that Bauters provides the potential factors or combination of factors contributing to restenosis, and that SMC proliferation is one of the alleged factors that may influence the status of the endothelium. One skilled in the art would not be left with the suggestion that administration of a specific amount of 17-beta estradiol with a device at an injured site would improve reendothelization and vascular endothelial function following vascular injury.

The Examiner disagrees because Bauters et al. teaches the connection between restenosis/smooth muscle proliferation and reendothelization, in that there is a cross-talk between endothelial cells and smooth muscle cells. Particularly, neointimal thickness is closely related to the presence of a regenerated endothelium. Indeed, intimal areas that are rapidly covered by continuous endothelium are protected from the accumulation of intimal SMCs (smooth muscle cells), whereas typical intimal hyperplasia occurs in areas where re-endothelialization is delayed (see page 108, column 2, growth regulatory properties of endothelial cells, lines 1-13). Dysfunctional

regenerating endothelium may contribute to the development of thickened intima because SMC proliferation. There are documented cases that demonstrate retardation of endothelial cell recoverage over damaged as opposed to normal media (see page 109, column 1, lines 3-11). In other words, since restenosis is reduced by the inhibition of proliferation of SMCs as taught by O'Brien et al., and the proliferation of SMC's are related to the dysfunctional regenerating endothelium (i.e. reendothelialization) as taught by Bauters et al., then one of ordinary skill in the art would find it obvious to treat a patient with 17β estradiol or its derivatives to improve reendothelialization since Ungs discloses that 17β estradiol reduces restenosis as well as O'Brien discloses that estrogen reduces restenosis.

In summary, Ungs teaches that estrogen compounds can be applied to the lumen of the blood vessel to increase blood flow and reduce chances of restenosis. Additionally, the estrogen compounds can be applied by a stent or balloon. O'Brien teaches the properties of estrogen compounds, in which improve endothelial function, reduce restenosis, and inhibits SMCs. Bauters teaches the connection between restenosis/smooth muscle proliferation and reendothelization, in which proliferation of SMCs are related to the dysfunctional regenerating endothelium (i.e. reendothelization). Thus, by improving endothelial function and inhibiting the proliferation of SMCs with estrogen compounds, one skilled in the art would have reasonable expectation that reendothelization would increase. The amounts of the estrogen compound are addressed below.

> The Appellant argues that none of the references discloses or suggests the amount of 17-beta estradiol in and effective amount to improve reendotheliazation and vascular endothelial function.

The Examiner respectfully disagrees, and notes that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Furthermore, it is considered that one of ordinary skill in the art at the time the invention was made would have found it obvious to vary and/or optimize the amount of 17β-estradiol provided in the method, according to the guidance provided by Ungs, in view of O'Brien et al., in further view of Bauters et al. to provide the desired treatment, such as the desired reduction in restenosis. It is noted that "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955.)

> The Appellant argues that Pitha is relied on merely as suggesting that hydroxypropyl-beta-cyclodextrin may be used to solubilize estradiol, but this is for topical, parenteral, oral or buccal preparations. None of these are for coated tents or PTCA.

The Examiner disagrees because Pitha not only teaches that hydroxypropyl-beta-cyclodextrin provides the desired solubility, but good absorption characteristics of the estradiol (see column 2, lines 62-68 and column 4, lines 64 through column 5, line

5). Although the routes of administration are different, in order to apply the estradiol to the stent or device, one skilled in the art could dissolve the estradiol first before applying it to the device. More importantly, the fact that hydroxypropyl-beta-cyclodextrin allows the estradiol to be absorbed in the body effectively is a good characteristic for one skilled in the art when considering using the estradiol as a drug.

> The Appellant argues that Fontana does not remedy the defects in Ungs because Fontana teaches a different compound and it is not administered in a device at an injured site to improve reendothelization and vascular enothelial function following vascular injury.

The Examiner disagrees because Fontana is used as a reference to teach an effective amount of estradiol derivatives used in the method of inhibiting aortal smooth muscle cell proliferation, particularly restenosis, in humans (see abstract). The compounds are administered after medical procedures such as angioplasty (see column 5, lines 11 and 12). The current claims rejected include 17-beta estradiol or derivatives, thus the Fontana reference applies the rejected claims. Ungs provides the teaching of that estrogen compounds can be placed on a device to reduce restenosis.

> The Appellant argues that Grainger et al. teaches totally different structures than estrogens and does not teach administration at an injured site to improve reendothelization and vascular enothelial function following vascular injury.

The Examiner disagrees because Grainger provides further teaching that drugs can be applied to injured areas to increase reendothelization by inhibiting SMCs.

Particularly, Grainger et al. teaches compounds to treat vascular traumas of differing severity, such as to prevent vascular rejection following graft or transplant, while larger doses are sufficient to treat more extensive vascular trama, such as restenosis following angioplasty (see column 34, lines 4-10). A biodegradable stent with the therapeutic agent impregnated therein can further be coated with a biodegradable coating having the therapeutic agent dispersed therein (see column 38, lines 27-30). Intravascular stents also provide a mechanical means of providing an increase in luminal area of a vessel (see column 38, lines 36-38). Furthermore, the placement of intravascular stents comprising a therapeutic agent which is an inhibitor of smooth muscle cell proliferation can provide increased efficacy by reducing or preventing intimal proliferation. This inhibition of intimal smooth muscle cells and stroma produced by the smooth muscle and pericytes can allow more rapid and complete re-endothelization following the intraventional placement of the vascular stent. The increased rate of re-endothelization and stabilization of the vessel wall following stent placement can reduce the loss of luminal area and decreased blood flow which is the primary cause of vascular stent failures (see column 38, liens 39-50).

In summary, Ungs may not specifically teach a method of improving reendothelization and vascular endothelial function, but Ungs teaches 17β-estradiol reduces restenosis. Fontana teaches that estrogen derivatives reduces restenosis and particularly inhibits aortal smooth muscle cell proliferation. Grainger et al. provides the teaching to connect restenosis, smooth muscle cell proliferation and improving

reendothelization and vascular endothelial function. Thus, a method of improving reendothelization and vascular endothelial function is rendered obvious by Ungs in view of Fontana and in further view of Grainger et al.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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